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New Methods

Quantitation of Basal Dyssynchrony and Acute Resynchronization from Left or Biventricular Pacing by Novel Echo-Contrast Variability Imaging

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OBJECTIVES This study sought to test a novel echocardiographic method based on contrast variability imaging (CVI), to quantify cardiac dyssynchrony and magnitude of resynchronization achieved by left ventricular (LV) and biventricular (BiV) pacing therapy.

BACKGROUND Left ventricular or BiV pacing is a promising new therapy for patients with heart failure and intraventricular conduction delay. However, precise quantitation of the extent of resynchronization achieved remains scant.

METHODS Ten patients treated with BiV or LV pacing therapy were studied. Echo-contrast was infused slowly, and gated images were acquired before and during contrast appearance. The temporally normalized variance derived from 30 to 50 sequential beats was determined at each pixel to yield the CVI image—displaying improved wall delineation. Systolic regional fractional area of radial sectors was calculated with active and temporarily suspended (AAI) pacing. All analyses were performed blinded to both patient and treatment.

RESULTS Pacing increased septal inward motion from $-20.4 \pm 9.6\%$ to $-30.5 \pm 14.0\%$, whereas lateral wall motion occurred earlier with no net magnitude change. Both spatial and temporal dyssynchrony in the LV declined nearly 40% with LV or BiV pacing ($p \leq 0.001$), and this correlated with increasing ejection fraction (31% to 39%; $p < 0.02$; $p < 0.004$ for correlation with dyssynchrony).

CONCLUSIONS The new imaging and regional dyssynchrony analysis methods provide quantitative assessment of resynchronization analogous to that previously obtained only by tagged magnetic resonance imaging. This could provide a useful noninvasive method for both identifying candidates and following long-term therapy. (J Am Coll Cardiol 2002;39:2052–8) © 2002 by the American College of Cardiology Foundation

Biventricular (BiV) or left ventricular (LV) pre-excitation is a promising new therapy for the treatment of patients with dilated cardiomyopathy (DCM) and contractile dyssynchrony due to intraventricular conduction delay (1–5). Prior studies have reported improved global LV systolic function (6–9), enhanced right-left heart synchrony (10), reduced pulmonary wedge pressure (8,9) and decreased mitral regurgitation (11). The central tenet of this therapy is that it recoordinates LV wall contraction, yet direct assessment of resynchronization itself has only recently been made (12,13) and objective quantitation remains somewhat difficult.

The most comprehensive analysis of mechanical dyssynchrony was achieved with three-dimensional magnetic resonance imaging (MRI) tagging (14–16), revealing early septal circumferential shortening followed by late stretch as lateral wall shortening began. In humans, however, this method could not be employed after pacemaker implantation. Investigators have since used tissue Doppler (12,13,17), focusing on patterns of systolic and postsystolic velocity direction. Such analysis has been generally semi-quantitative and limited to longitudinal motion.

We recently developed an alternative approach. This echocardiographic method exploits the temporal statistical variance of pixel intensity induced when contrast microbubbles mix into the ventricular cavity (18). Regions with sudden bubble appearance (i.e., blood pool) display high variance, whereas myocardial tissue has far less. Setting pixel intensity to reflect this variance yields a high contrast image (similar to X-ray ventriculography) derived from 30 to 50 sequential beats, and can greatly enhance delineation of the myocardial wall/blood pool interface (18). Herein, we test the utility of this method to quantify dyssynchrony and resynchronization effects from LV or BiV pacing, and examine their correlation with LV ejection fraction (EF).

METHODS

Study population. Ten patients with DCM (mean end-diastolic dimension of 6.9 ± 0.7 cm) and left bundle-type conduction delay were studied. All subjects were in New York Heart Association functional class III or IV, in normal sinus rhythm, with an EF <35% based on left ventriculog-

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Abbreviations and Acronyms

BiV = biventricular pacing
CVI = cardiac variability imaging
DCM = dilated cardiomyopathy
EF = ejection fraction
LBBB = left bundle branch block
LV = left ventricle
MRI = magnetic resonance imaging
RFAC = regional fractional area change

raphy at time of pacemaker implantation. No subject had a standard indication for pacemaker treatment. Mean age was 56 ± 8 years and QRS duration was 169.4 ± 22.8 ms. Six subjects had nonischemic disease. Invasive hemodynamics from seven subjects were reported previously (14). All patients provided informed consent, and the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions approved the protocol. Patients received chronic LV-only pacing (n = 7; Medtronic Kappa 400 or 700, Minneapolis, Minnesota) with the lead in a lateral or anterolateral vein, or BiV pacing (n = 3; CONTAK-TR, Guidant, Indianapolis, Indiana) with the LV lead in the same location and a second lead at the right ventricular apex. Patients were studied once 8.8 ± 11.9 months after initial implantation. The study group comprised nearly all available subjects treated with this therapy at Johns Hopkins Hospital over the past two to three years, with death or intervening cardiac transplant removing several subjects.

Echocardiographic protocol. Echo contrast (Optison, Mallinckrodt, Hazelwood, Missouri) was diluted in normal saline solution (5% to 40%) and injected intravenously at 1 ml over 30 s, followed by saline solution flush. Gated echocardiographic images (25 to 30 Hz) were obtained (Sonos 5500, Agilent, Massachusetts) using automatic electrocardiogram R-wave detection. Images were acquired before and during initial contrast mixing into the LV (e.g., first pass). Two sets of images (25 to 30 Hz) were obtained: active ventricular pacing (VVI mode, with atrial tracking and ventricular pre-excitation, mean atrioventricular delay = 97 ± 23 ms), and pacing off (AAI mode at identical heart rate). Images were obtained after 10 min of stabilization with each mode, as studies have shown transient changes with LV or BiV pacing stabilize within minutes (6,19).

CVI analysis. Cardiac variability images (CVI) were generated as recently described (18). Briefly, 30 to 50 consecutive images were digitally recorded, gated to cardiac cycle phase (time from prior R-wave). At each phase and for each pixel, the temporal average and variance were determined from the total set of cycles. Setting pixel intensity to the variance/mean ratio generated the CVI image, and while depicting a single beat, the image was derived from many steady-state cycles. Figure 1 shows a typical CVI image in the apical four-chamber view. The raw LV image with or without contrast (Fig. 1A and 1B) demonstrates the indistinct endocardial borders that can often complicate boundary delineation. However, the CVI image displays substantial contrast enhancement of the blood pool (Fig. 1C) versus a darker myocardium, as the temporal variability induced by the microbubbles is greater within the blood. This image is then processed to yield contour tracings using custom software (Fig. 1D).

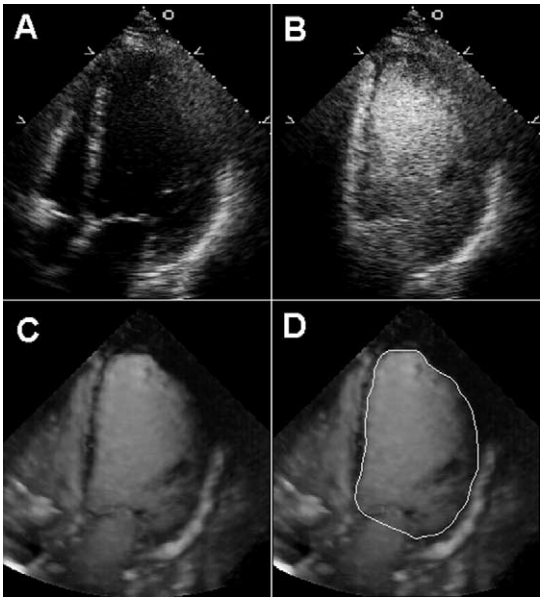

Figure 1. Comparison between raw echo-image obtained prior to contrast injection **(A)**, unprocessed image after opacification with contrast agent **(B)** and cardiac variability imaging (CVI)-processed image **(C)**. The CVI method enhanced contrast between the blood pool and myocardial wall to improve quantitation of endocardial motion. **Panel D** shows the superimposition of the traced endocardial border.

For the accompanying video to Figure 1, please see the June 19th issue of *JACC* at www.cardiosource.com/jacc.html

Contour analysis. Contours were independently generated by two experienced echocardiographers (M. K., H. S.), fully blinded as to patient source and pacing condition, and drawn using custom software that linked identified points, with papillary muscles included in the LV volume to standardize measurements. The image corresponding to the QRS peak defined end-diastole, and image with the smallest area was end-systole. A third independent observer then reviewed all contours—superimposing them on the CVI image and viewing them in cine-mode. Most were very similar, and subsequent analyses averaged results from both sets. Clear discrepancies between contour sets were observed in 25%, and when viewed simultaneously and superimposed on the CVI image, one was believed to be more accurate by the third fully blinded observer. In these instances, only one contour set was analyzed. We have shown previously that interobserver variability of contour-derived indexes declines significantly from 18% to 8% with CVI, while intraobserver variability falls from 8% to 4.3% (18).

Left ventricular contours were analyzed using a fixed axis system with the centroid as the center point, using the regional area method (20,21). The LV was divided into 24, 15° pie-sectors (Fig. 2A, typically 14 to 16 sectors within both septal and lateral regions). Regional fractional area

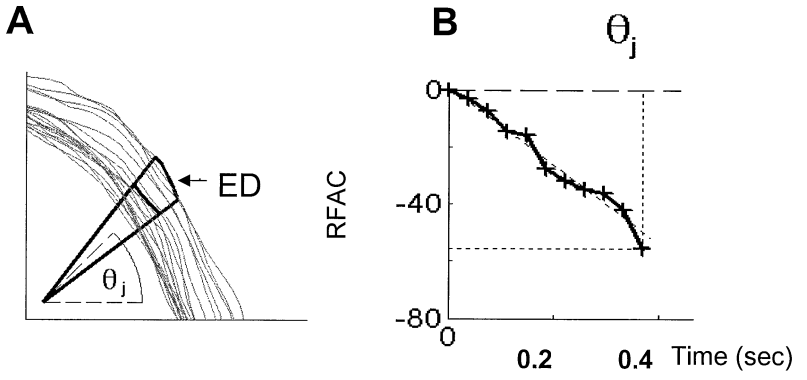

Figure 2. Determination of regional fractional area change (RFAC). **(A)** A pie-shaped sector is drawn from the centroid of each contour to 15° arcs on the contour. Sector area is determined and referenced to its value at end-diastole (corresponding to QRS peak) to derive RFAC. **(B)** Example of RFAC versus time from end-diastole to end-systole, for an example sector.

change (RFAC) for each sector was determined in each CVI frame, normalizing regional fractional area to the value at end-diastole. The RFAC for each sector was plot versus time to yield displacement maps (Fig. 2B), analogous to circumferential strain plots previously derived by MRI tagging (14–16).

Average systolic motion in septal versus lateral regions was determined from RFAC and rate of RFAC averaged from all relevant sectors within each respective territory (Fig. 2B). Spatial mechanical dyssynchrony was equal to the coefficient of variation of RFAC at time of maximal negative RFAC (based on all myocardial sectors, i.e., excluding valve apparatus), similar to an index developed for MRI images (14). Temporal dyssynchrony was calculated as the coefficient of variation of times at maximal negative RFAC from the same sectors. Global LV volumes and EF were determined from four-chamber CVI images, using the area-length method.

Statistical analysis. Data are reported as mean ± SD. Multiple RFACs assessed in each heart were combined as an average (mean RFAC) or variance (dyssynchrony index) employing the same number of segments in each estimate. This index was then determined in each patient under AAI and VDD pacing modes, and compared using a paired *t* test or Wilcoxon test where appropriate.

RESULTS

Regional mechanical function from CVI images: pacing-on versus pacing-off. Seventeen of the 20 CVI images could be analyzed (9 four-chamber views, 8 short-axis views). The three excluded views had very poor image quality or far-wall attenuation from the contrast injection that prevented delineation of the lateral wall. Figure 3 displays a representative four-chamber CVI image for LV pacing on versus off, with regional sectors delineated. A cine version of this image is available at the internet site and shows discoordinate septal motion that improves with lateral wall stimulation. Corresponding RFAC-time plots are displayed in Figure 4A. These were characterized by early septal shortening followed by late-systolic dyskinesis, and early lateral stretch followed by late shortening—similar to results previously obtained by tagged MRI (14). With lateral wall pre-excitation (pacing on), RFAC became negative in all sectors. Septal regions now displayed enhanced contraction, while lateral regions showed a similar magnitude of contraction but an earlier phase.

Mean data are displayed in Figure 4B. Both the magnitude (−20.4 ± 9.6%—off; −30.5 ± 14.0%—on, $p = 0.008$, 50% increase) and rate of RFAC (−26.4 ± 35.5 vs. −63.8 ± 52.5, $p = 0.01$, 140% increase) significantly improved in the septal territory with LV or BiV stimulation. In contrast, neither was significantly altered in the lateral wall, although timing was earlier. Interestingly, we found no late-systolic stretch of the lateral wall despite frequent use of LV-only pacing.

Mechanical intraventricular dyssynchrony. Spatial dyssynchrony declined with LV or BiV stimulation to 53.5 ± 31.1 from 83.5 ± 28.5 with AAI pacing ($p < 0.0001$, dimensionless, Fig. 5A). This was observed in both four-chamber (76.6 ± 20.9 to 47.9 ± 19.3, $p = 0.007$) and short-axis views (91.4 ± 34.9 to 59.9 ± 41.2, $p < 0.03$), although it tended to be more consistent in the former. Temporal dyssynchrony also declined with ventricular stimulation (22.5 ± 12.2 vs. 36.5 ± 12.0, $p = 0.001$, Fig. 5B), and this too was observed in both views (22.2 ± 10.8 vs. 35.0 ± 12.6, $p = 0.05$ for four-chamber views; 22.3 ± 13.3 vs. 38.2 ± 11.9, $p = 0.005$ for short-axis views). Thus, both special and temporal LV mechanical dyssynchrony was improved by 35% to 40% with LV (or BiV) stimulation, and this was observed in most all subjects. There was no significant difference in dyssynchrony measures between ischemic and nonischemic patients.

Global function also improved, with a rise in EF from 31.1 ± 5.6% in AAI mode to 38.8 ± 8.6% with VDD pacing ($p < 0.02$, Fig. 5C). This inversely correlated with spatial dyssynchrony ($p < 0.004$, Fig. 5D). End-diastolic volume did not significantly change (305.0 ± 106 ml AAI; 282.0 ± 63 ml VDD, $p > 0.25$), whereas there was a trend toward reduced end-systolic volume with active stimulation

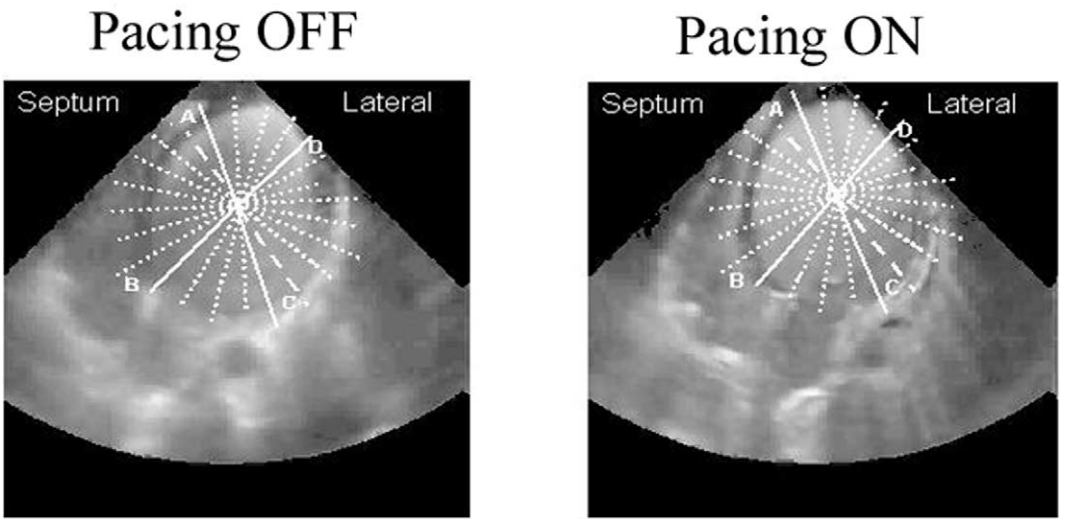

Figure 3. Representative four-chamber cardiac variability imaging (CVI) images generated with stimulation (left ventricular [LV] only in this case) turned on or off. With pacing suspended, there was septal-apical dyskinesis characterized by early shortening followed by late systolic stretch. With LV lateral wall stimulation, dyskinesis declined and overall ejection improved. The radial lines on the initial still image delineate the sectors within the septum and lateral wall that were used for subsequent regional fractional area change analysis (see Fig. 4).

For the accompanying video to Figure 3, please see the June 19th issue of *JACC* at www.cardiosource.com/jacc.html

(206.6 ± 70.9 ml AAI vs. 173.8 ± 52.1 ml VDD, p = 0.08).

DISCUSSION

We present novel echo-contrast and regional wall synchrony analysis to obtain rigorous quantitation of basal discoordination and resynchronization effects achieved in heart failure patients with basal conduction delay treated with LV or BiV pacing. Using the newly developed CVI imaging method to enhance wall detection, dyssynchrony was shown to decline by 40% with these pacing modalities, a change that inversely correlated with EF. The dominant changes were a decline in septal dyskinesis and earlier lateral wall shortening. Importantly, this regional analysis was performed fully blinded to subject and condition.

Comparison to prior studies. Only a few published studies have quantified regional wall motion in patients with heart failure subject to BiV pacing. Kerwin et al. (10) were among the first, employing radionuclide gated images to examine interventricular timing, and finding that BiV pacing improved interchamber synchrony. However, this is not necessarily the same as the intraventricular dyssynchrony which has been shown to predict mechanical improvement with pacing (14). Two-dimensional echocardiography images can assess global function but have often proven inadequate for quantifying dyssynchrony (2,3). Three-dimensional echocardiography provides more detailed global assessments, but has not yielded quantitative analysis (22).

Tissue Doppler has been used recently to examine synchrony from BiV pacing (12,13,17). For example, Yu et al. (13) recently reported improved chronic synchrony based on variable peak velocity times about the LV. Dyssynchrony is often presumed when systolic reversal of velocity direction or postsystolic contraction is observed, with a tally of the number of such segments yielding the dyssynchrony index. However, this has been based on longitudinal motion, and while parasternal long-axis views can image posterolateral and septal walls, the former is not typically the location of the LV pacing lead. To our knowledge, the present study is the first to provide synchrony data from a cohort of subjects treated mostly with LV-only pacing.

The CVI method employed conventional imaging in an apical four-chamber view, making radial motion analysis possible. We have previously shown that CVI imaging reduces interobserver and intraobserver variance for assessment of the endocardial contour and calculation of global chamber parameters (18). Wall motion analysis can be performed without contrast, although the quantitation required to derive a useful dyssynchrony parameter is often difficult to achieve, particularly given small motion in DCM hearts. Cardiac variability imaging significantly enhanced contour analysis in 50% of normal subjects (18), and in the present DCM patients, CVI salvaged what would otherwise have been untraceable images in nearly 40% of cases. About 30 s is required to derive the CVI image from recorded data. Contouring takes somewhat longer (15 to 20 min), but this could be improved by using more sophisticated automatic tracking algorithms.

Importance of dyssynchrony. Substantial mechanical dyssynchrony exists in subjects with DCM and left bundle branch block (LBBB)-type conduction delay (14,23), and is a strong correlate with acute mechanical improvement from pacing (14). Recent data indicate that patients with improvement in dyssynchrony by BiV pacing also experience clinical improvement in exercise performance and symptoms (12). There is growing recognition that an identification of treatment candidates based solely on QRS duration is inadequate (14), whereas inclusion of some direct measure

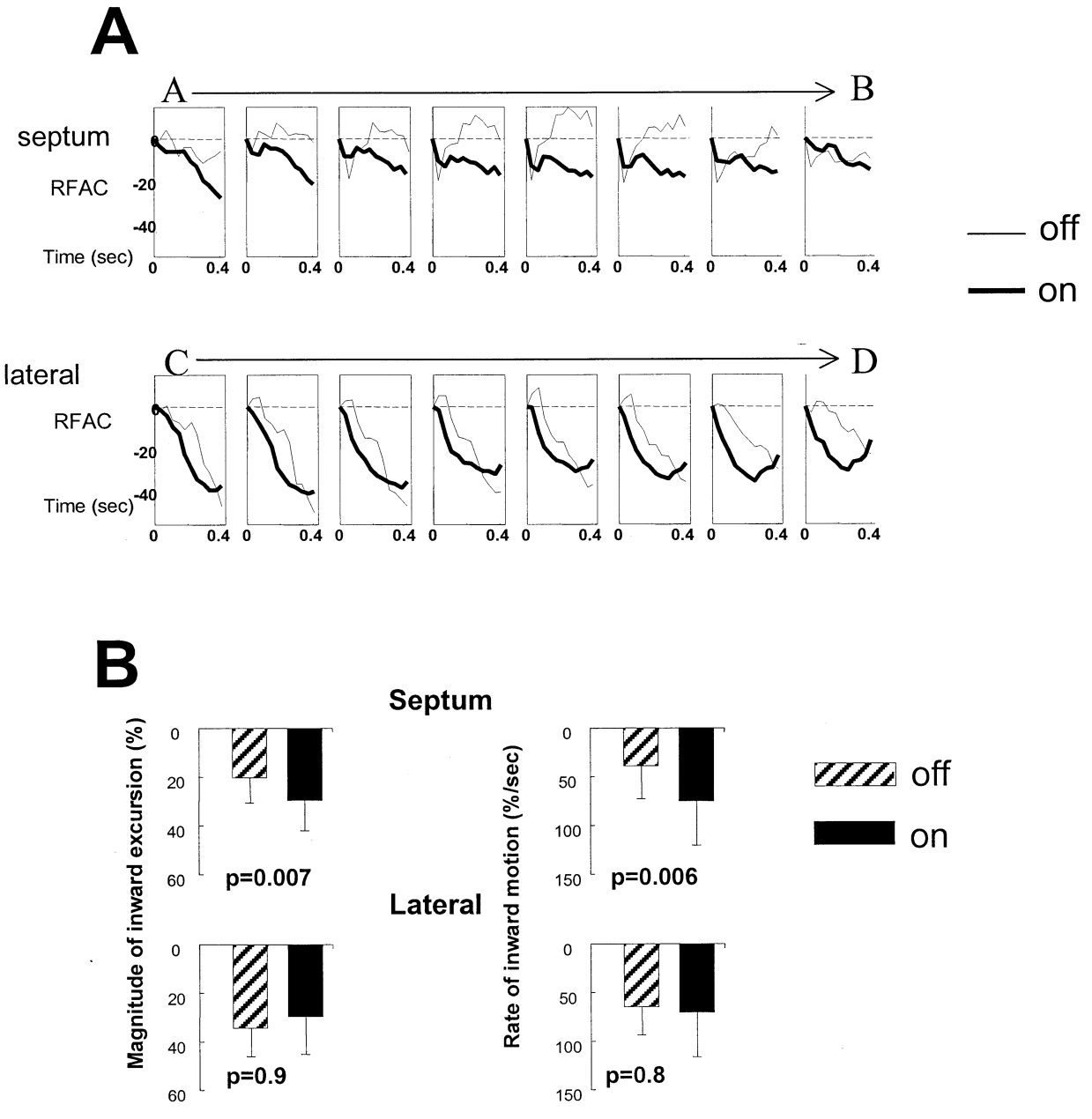

Figure 4. **(A)** Regional fractional area change (RFAC) maps for each sector corresponding to the cardiac variability imaging images shown in Figure 3. The location of each segment is identified in the prior figure. In normal sinus rhythm (stimulation off), septal contraction often displayed early negative RFAC followed by late positive deflection (expansion) and lateral contraction showed the opposite pattern. Left ventricular pacing improved motion in the septum toward normal but had minimal effects on lateral wall motion. **(B)** Mean results for maximal RFAC and mean rate of change in septal and lateral regions with stimulation activated or turned off. See text for details.

of dyssynchrony assists in identifying responders. The RFAC maps and indexes derived in the present analysis are quite similar to the strain data obtained by MRI tagging (14), and may prove useful in this regard.

Mechanical dyssynchrony with a LBBB-type conduction pattern involves both early activation of the septum followed by late systolic stretch, with late-lateral activation at higher loads. Both reduce net chamber efficiency, and BiV and LV pacing improve both systolic function (6–9) and efficiency (19). The present data highlight normalization of septal motion rather than enhanced lateral motion as a principal kinematic feature of these effects. The lack of concomitant improvement in net lateral wall shortening—even in subjects with solely LV pacing—indicates that timing rather than shortening magnitude in this region is the major factor underlying improvement. Left ventricular only pacing did not produce dyssynchrony in the opposite direction, but rather helped prevent early septal shortening and late distention.

Study limitations. This study was not designed to test whether changes in dyssynchrony at baseline predict long-term pacemaker efficacy or to examine long-term effects of

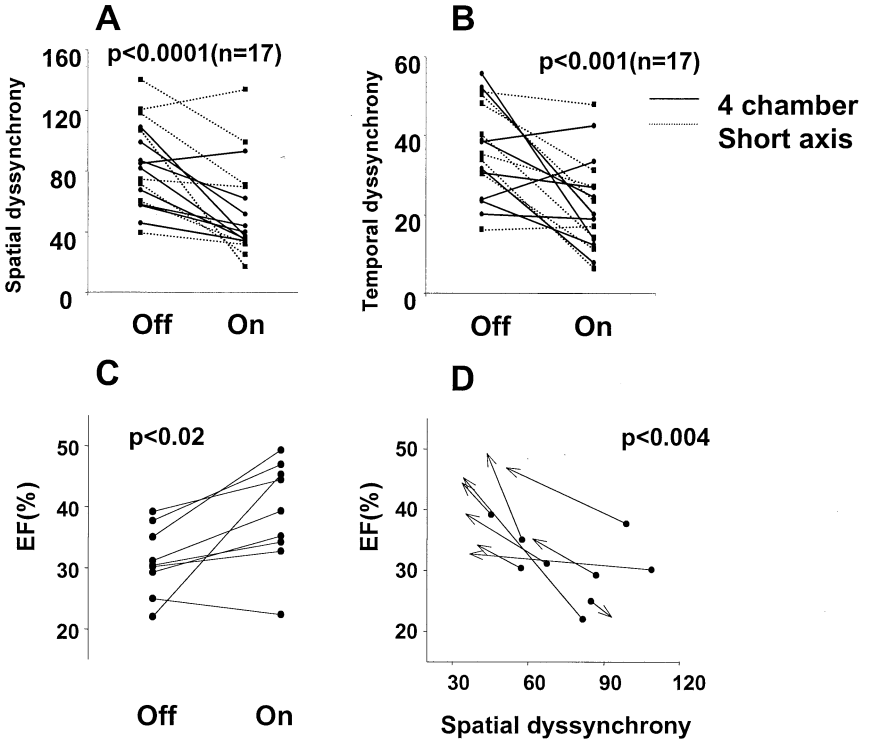

Figure 5. Quantitation of ventricular mechanical dyssynchrony. **(A)** Spatial dyssynchrony; a coefficient of variation of regional fractional area change (RFAC) measured at the time of maximal negative RFAC; **(B)** temporal dyssynchrony; a coefficient of variation of time at maximal negative RFAC; left ventricular (LV) or biventricular (BiV) pacing significantly improved both measures in nearly all patients. **(C)** Improvement in EF induced by LV or BiV pacing. **(D)** There was a negative correlation between the extent of spatial dyssynchrony and systolic function, and most all subjects showed a shift upward and to the left with active pacing; $p = 0.005$, $n = 9$. EF = ejection fraction.

the therapy on synchrony. This would require a larger patient cohort, and we did not have the CVI analysis developed at the time many of the patients first received their pacing system.

High contrast CVI images often revealed papillary muscles and myocardial trabeculae, and these features could introduce errors into the assessment of radial contraction due to nonradial motion (e.g., circumferential or torsional deformation). To avoid this, a smooth tracing was manually passed through the base of protruding papillary muscles and trabeculae. This introduced some subjectivity and user-dependence, but was needed for reliable assessment of radial contraction and dyssynchrony. Also, the CVI method could not correct for excessive contrast that can result in image loss in the far-field wall due to attenuation (24). We did not obtain independent stroke volume data to confirm enhanced ejection independent of the echo-derived images. Thus, we cannot eliminate shape changes during isovolumic contraction as contributors to the EF improvement, although volume data did suggest reduced end systolic volumes.

Comparisons between LV-only and BiV pacing on dyssynchrony would be interesting and important; however, this requires unpaired analyses with many more subjects per group and, thus, awaits multicenter studies. Lastly, we did not obtain data from subjects with DCM but normal contractile coordination. Such information should prove useful for defining patients with narrower QRS complexes who nevertheless have substantial dyssynchrony, and those with a wide QRS that might principally stem from right ventricular delay and, thus, not belie LV dyssynchrony.

CONCLUSIONS

In summary, we provide a new approach to assessing regional dyssynchrony, and demonstrate that LV-only (or BiV) improves dyssynchrony by nearly half in patients with DCM and intraventricular conduction delay. This is largely manifest by offsetting paradoxic septal motion while preserving lateral wall motion. The new echo-contrast method and analysis may be useful for stratifying patients with dyssynchrony, and following therapeutic efficacy.

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